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(54) Title: SUSTAINED-RELEASE FORMULATION OF D-THREO-METHYLPHENIDATE

(57) Abstract

A sustained-release formulation of *d-threo*-methylphenidate (dtmp).

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SUSTAINED RELEASE FORMULATION OF D-THREO-METHYLPHENIDATE

Field of the Invention

This invention relates to a sustained-release formulation of methylphenidate.

Background of the Invention

Methylphenidate is a known drug. It is used primarily to treat hyperactive children. It is a controlled substance.

Methylphenidate is a chiral molecule. The properties of the enantiomers have been investigated to some extent, although the drug is still administered as the racemate. It is generally thought that *d-threo*-methylphenidate (abbreviated herein as dtmp) is the active material, and that its antipode (ltmp) is metabolised more rapidly.

Methylphenidate is often administered in a sustained-release formulation. For example, a coated tablet comprising racemic methylphenidate is administered, with a view to maintaining a therapeutically-effective level of the drug in circulation. This formulation does not provide satisfactory or reproducible dosing.

Srinivas *et al*, Pharmaceutical Research 10(1):14 (1993), disclose a further disadvantage of known methylphenidate sustained-release formulations, i.e. that serum levels of the drug are increased by chewing. Many children chew tablets, and are therefore liable to receive an unnecessarily high dose of a controlled substance.

Patrick *et al*, Biopharmaceutics and Drug Disposition 10:165-171 (1989), describe the absorption of sustained-release methylphenidate formulations compared to an immediate-release formulation. It is suggested that the optimum dosage of methylphenidate for children is 0.5-0.7 mg/kg/day.

Summary of the Invention

The present invention is based on an appreciation of the fact that, although it is possible to provide a model of chiral drug distribution, and measure the concentration of individual enantiomers and their breakdown products in

a subject, over time, this is a poor model for understanding the effectiveness of the enantiomers. Since, after an initial period, the sustained-release formulation should ideally release the active material as evenly as possible, the administration of a racemate, i.e. of two related compounds, takes no account of interaction between the enantiomers. According to this invention, it has surprisingly been found both that there is considerable interaction, and that dtmp provides relatively linear kinetics within the clinically effective dose range in a suitable model, and is therefore suitable for incorporation in a sustained-release formulation. The experiments and data on which this discovery is based are given below.

Description of the Invention

The dtmp that is used in this invention is substantially free of its antipode (ltmp), e.g. in an enantiomeric excess (ee) of at least 70%, preferably at least 90%, and more preferably at least 95%. The dtmp may be substantially enantiopure. It may be used in the form of any suitable salt, e.g. the hydrochloride.

The dtmp may be administered by the same means as is known for racemic methylphenidate, in a sustained-release formulation, e.g. a coated tablet. It may be administered in any other conventional sustained-release formulation, via any suitable route of administration. Conventional dosing parameters may be adopted, i.e. those which are known to or adapted to the practice of those skilled in the art.

Compositions of the invention may be administered for known purposes, e.g. the treatment of attention-deficient hyperactivity disorder (ADHD; this term is used herein to encompass attention-deficit disorder) in pre-pubertal children and in adults, as a stimulant in cancer patients treated with narcotic analgesics, and also for the treatment of depression (e.g. in AIDS patients), compulsive shopping disorder, narcolepsy and hypersomnia. By contrast to known formulations of methylphenidate, the present

invention may have any or all of the following advantages: linear kinetics within the clinically effective dose range, the reduction of exposure to a controlled substance, reduced side-effects (which include anorexia, insomnia, stomach ache and headache), reduced abuse potential, reduced C_{max}, a reduced level of active material even when chewed, reduced patient variability, reduced interaction with ltmp or other drugs, and less variability between fed and fasted subjects.

By controlling the nature of the formulation, it is possible to control dissolution *in vitro*, and thus match or exceed the US National Formulary (NF) drug release profile for methylphenidate hydrochloride. Further, when administered to a healthy subject, a serum level of dtmp can be attained that is at least 50% of C_{max}, over a period of at least 8 hours, e.g. 8-16, 8-12 or 8-10 hours. Thus, for example, a shorter release period may be preferred or a different period before the serum level drops below a different proportion of C_{max}.

The serum level may be also controlled so that it remains high during the day, after taking a dosage in the morning, and is reduced in the evening, before it can have any undesirable effect on sleeping patterns. Preferably, the serum level is at least 50% C_{max} after 8 hours and less than 25% C_{max} after 12 to 16 hours.

A formulation of the invention may be a unit dosage such as a tablet, capsule or suspension. It may be in matrix, coating, reservoir, osmotic, ion-exchange or density exchange form. It may comprise a soluble polymer coating which is dissolved or eroded, after administration. Alternatively, there may be an insoluble coating, e.g. of a polymer, through which the active ingredient permeates, as from a reservoir, diffuses, e.g. through a porous matrix, or undergoes osmotic exchange. A further option for a sustained-release formulation involves density exchange, e.g. in the case where the formulation alters on administration, e.g. from microparticles to a gel, so that

the active ingredient diffuses or permeates out. Ion-based resins may also be used, the active component being released by ionic exchange, and wherein the rate of release can be controlled by using cationic or anionic forms of the drug.

It is preferred to use a formulation in this invention that is resistant to chewing, e.g. micronised particles that are individually coated and which do not immediately release the active component on chewing, or possibly even actively discourage chewing by their consistency. The various effects etc may be due to the use of dtmp and/or the absence of ltmp.

Comparative Pharmacodynamics of *d-threo*-methylphenidate and Racemate

The study design was based on that described by Aoyama *et al*, J. Pharmacobio-Dyn. 13:647-652 (1990). Male Wistar rats were dosed with methylphenidate hydrochloride or its d-isomer at nominal dose levels of

racemate: 1.5, 3, 4.5 or 6 mg base/kg body weight
d-isomer: 0.75, 1.5, 2.25 or 3 mg base/kg body weight

Blood samples were taken pre-dose, and 7 min, 15 min, 30 min, 45 min, 1 h, 1.5 h, 2 h, 3 h, 4.5 h, 6 h, 8 h post-dose. The samples were centrifuged to separate the plasma. Plasma samples were assayed for dtmp, by liquid chromatography mass spectrometry.

The results are shown in the accompanying drawing. Figure 1 gives a comparison of the AUC (area under the curve) for values, obtained from plasma concentration of dtmp, versus time, for dtmp and methylphenidate (at equivalent dtmp quantities) dosed at a range of dtmp concentrations. Both curves show non-linear kinetics, evident as a point of disjunction in each curve. As the doses administered are increased, the quantity absorbed (i.e. AUC) increases in a linear fashion, until the disjunction, when the absorbed quantity is dramatically

increased. This disjunction occurs within the clinically-relevant range (16-140 mg.h/ml in humans) for racemate dosing, but, surprisingly, is outside of this range for dtmp dosing.

This means that conventional dosing of the racemate, which involves increasing amounts of the drug, cannot be satisfactorily controlled. The possibility exists that a dosage will be given that is unnecessarily high.

Administration of dtmp has a surprising beneficial effect, in that a relatively linear dtmp AUC level in serum (lower curve) is achieved within the clinically-relevant range. The point of disjunction occurs outside the clinically-relevant range and, therefore, the flux of drug into and out of the circulatory system is more controllable. This makes dtmp suitable for incorporation in a sustained release formulation.

CLAIMS

1. A sustained-release formulation of *d-threo*-methylphenidate (dtmp).

2. A formulation according to claim 1, which meets, or exceeds in terms of slower dissolution, the NF drug release profile for methylphenidate hydrochloride.

3. A formulation according to claim 1 or claim 2, which comprises less than 20 mg dtmp per unit dosage.

4. A formulation according to claim 3, which comprises less than 15 mg dtmp per unit dosage.

5. A formulation according to any of claims 1 to 4, selected from those comprising a soluble, erodable or otherwise modified coating, and those having an insoluble coating through which the dtmp passes, in use.

6. A formulation according to any of claims 1 to 5, in which the dtmp is micronised.

7. A formulation according to any of claims 1 to 6, which (on average) when administered to (a sample of) healthy subjects, exhibits a serum level of dtmp of at least 50% C_{max}, over a period of at least 8 hours.

8. A formulation according to claim 7, wherein the period is 8 to 12 hours.

9. A formulation according to claim 7 or claim 8, wherein the serum level is less than 25% C_{max} after 12 to 16 hours.

10. A formulation according to any of claims 1 to 9, which on administration to a healthy subject, exhibits C_{max} of 2 to 20 ng/ml at a dosage of at least 2 mg.

11. A formulation according to any of claims 7 to 10, wherein C_{max} is substantially unaffected by chewing.

12. A method for treating a subject having a disorder capable of treatment using methylphenidate, which comprises administering to said subject a sustained-release formulation comprising dtmp in an amount sufficient to maintain a serum level of at least 50% of the maximum level, for at least 8 hours.

13. A method according to claim 12, wherein at least the initial dosage is less than 15 mg dtmp per day.

14. A method according to claim 12 or 13, wherein the subject is adult and the disorder is compulsive shopping disorder, narcolepsy or hypersomnia.

15. A method according to claim 12 or 13, wherein the disorder is attention-deficit hyperactivity disorder.

16. A method according to claim 12, wherein said amount is less than 1 mg/kg/day.

17. A method according to claim 12, wherein said amount is less than 0.5 mg/kg/day.

Chart 1

Comparison of AUC for d-isomer; d-isomer vs racemate dosing

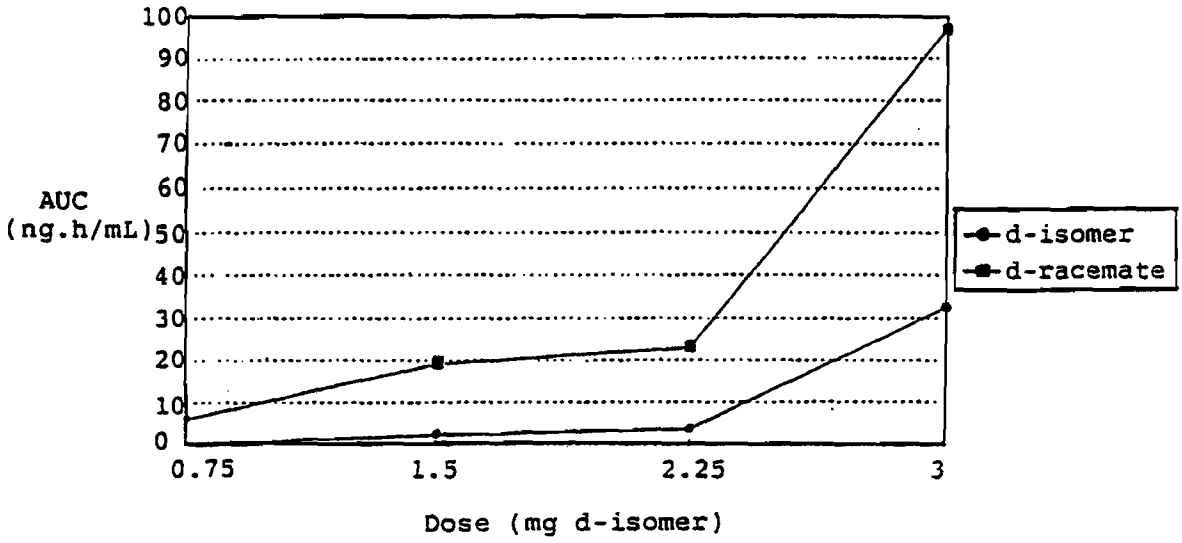

FIG. 1

INTERNATIONAL SEARCH REPORT

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PCT/GB 96/01690

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/445

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	J. PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, vol. 241, no. 1, April 1987, USA, pages 152-158, XP000612231 PATRICK ET AL.: "Pharmacology of the Enantiomers of threo-Methylphenidate" see the whole document ---	1-17
A	PHARMACOLOGY, BIOCHEMISTRY AND BEHAVIOR, vol. 40, no. 4, December 1991, USA, pages 875-880, XP000612226 ECKERMAN ET AL.: "Enantioselective Behavioral Effects of threo -Methylphenidate in Rats" see the whole document -----	1-17

☐ Further documents are listed in the continuation of box C.

☐ Patent family members are listed in annex.

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1

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